REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
29-07-2009	Review Article	2008

4. TITLE AND SUBTITLE
Zinc and Diarrheal Disease: Current Status and Future Perspectives

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER
MISC08-24

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S Army Medical Research and Material Command
Fort Detrick
Frederick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release.
Distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Zinc plays an important role in modulating host resistance to infectious agents and reducing the risk, severity, and duration of diarrheal diseases. Zinc is important in the developing world and in low-income and middle-income countries where mild-to moderate zinc deficiency is highly prevalent. The WHO/UNICEF recommendations for zinc supplementation: 20mg zinc/day for 10–14 days for children with acute diarrhea and 10 mg/day for infants under 6 months of age. Effective forms include sulfate, gluconate, or acetate. No similar studies have been conducted on adults. Thus, carefully conducted clinical trials are necessary to ascertain the efficacy of zinc in prevention of acute and persistent diarrhea in adults. Faced with rising antibiotic resistance and the lack of effective antidiarrheal vaccines, oral zinc provides substantial benefit in the reduction of stool output and disease duration combined with safety, selectivity of action, and low cost. Thus, oral zinc supplementation is a practical therapeutic intervention for the treatment of diarrhea in children, and by extension, should be provided to adults.

15. SUBJECT TERMS
Cholera, diarrhea, enterotoxigenic Escherichia coli, HIV, shigellosis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Douglas Dauphinee
Unclassified	Unclassified	Unclassified	UL	7	19b. TELEPHONE NUMBER *(Include area code)* 508-233-4859

Zinc and diarrheal disease: current status and future perspectives

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Current Opinion in Clinical Nutrition and Metabolic Care 2008, 11:711–717

Purpose of review

To evaluate clinical data indicating the benefits of oral zinc supplementation to prevent and/or treat diarrhea in children and extend these findings to adults.

Recent findings

Zinc plays an important role in modulating host resistance to infectious agents and reducing the risk, severity, and duration of diarrheal diseases. Zinc is important in the developing world and in low-income and middle-income countries where mild-to-moderate zinc deficiency is highly prevalent.

The WHO/UNICEF recommendations for zinc supplementation are based on meta-analyses of randomized, controlled intervention trials on children: 20 mg zinc/day for 10–14 days for children with acute diarrhea and 10 mg/day for infants under 6 months of age. Effective forms include sulfate, gluconate, or acetate. No similar studies have been conducted on adults. Thus, carefully conducted clinical trials are necessary to ascertain the efficacy of zinc in prevention of acute and persistent diarrhea in adults.

Summary

Faced with rising antibiotic resistance and the lack of effective antidiarrheal vaccines, oral zinc provides substantial benefit in the reduction of stool output and disease duration combined with safety, selectivity of action, and low cost. Thus, oral zinc supplementation is a practical therapeutic intervention for the treatment of diarrhea in children, and by extension, should be provided to adults.

Keywords

cholera, diarrhea, enterotoxigenic *Escherichia coli*, HIV, shigellosis, zinc

Curr Opin Clin Nutr Metab Care 11:711–717

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Introduction

Diarrhea is a syndrome that is frequently not differentiated clinically by specific etiologic agent. Diarrhea remains a major public health problem, especially in children in developing countries, with approximately 1.5 billion episodes per year. It is estimated that diarrheal diseases cause 2 million deaths annually in children under the age of 5 years and contribute substantially to malnutrition in the surviving children [1]. The use of glucose-electrolyte oral rehydration therapy (ORS) has dramatically reduced mortality from dehydration caused by diarrhea – estimates of global mortality from diarrhea declined from approximately 4.6 million annual deaths during the mid-1980s to the current estimate of 2 million. In contrast, rates of morbidity as a result of diarrhea remain as high as ever [2]. Recently, Roy *et al.* [3] reported that the estimated rate of acute gastrointestinal illness (AGI) in the USA alone is 0.65 episodes per person-year. For this estimate, AGI was defined as at least three loose stools in a 24 h period resulting in an impairment of daily activities or diarrhea duration greater than 1 day. Thus, diarrhea represents a practical public health problem.

Diarrhea is caused by many pathogens. Enterotoxigenic *Escherichia coli* (ETEC), *Campylobacter*, and *Shigella* account for approximately 60% of bacterial pathogens causing travelers' diarrhea [4]. Additionally, limited vaccines to prevent diarrheal illness are available, and antibiotic-resistant diarrhea cannot be effectively treated with common antibiotics. In the absence of anti-diarrheal vaccines, development of alternative treatments that minimize incidence of and morbidity due to diarrhea in adults is necessary. An association between diarrhea-associated morbidity and zinc intake was first noted in early observational studies that documented increased fecal zinc loss, a negative zinc balance, and low tissue zinc concentrations among children with diarrhea. Conservative estimates suggest that at least 25% of the world's population is at risk of zinc deficiency [5]. Zinc deficiency is highly prevalent in developing countries because of inadequate dietary intake, lack of

 DOI:10.1097/MCO.0b013e3283109092

intake of animal foods, and/or reduced bioavailability of zinc because of a high phytate:zinc ratio in the diet [2]. The adverse effects of zinc deficiency on the immune response are likely to increase the susceptibility of children to infectious diarrhea, and chronic or persistent diarrhea may further compromise the zinc status because of increased fecal losses of zinc during diarrheal episodes [6]. A recent estimate of disease-specific and all-cause mortality attributable to zinc deficiency indicates that zinc deficiency was responsible for 453 207 deaths (4.4% of childhood deaths) and 1.2% of the burden of disease (3.8% among children between 6 months and 5 years) in Africa, Asia, and Latin America [2]. Similar data for adults are not available.

Zinc supplementation of children with acute and persistent diarrhea increases serum zinc concentration and helps them to maintain an improved zinc status during the convalescent period [7]. The recent WHO/UNICEF recommendations for zinc supplementation in children are based on a summary of scientific evidence [8]: 20 mg zinc supplements/day for 10–14 days for children with acute diarrhea and 10 mg/day for infants less than 6 months old. Each individual dose of zinc should contain 10 or 20 mg of elemental zinc. The zinc salt should be soluble in water – only zinc sulphate, zinc acetate, or zinc gluconate should be used. The most recent meta-analysis of randomized, controlled trials (RCTs) compared zinc supplementation with placebo in 22 studies involving children and the authors concur with the WHO/UNICEF recommendations: zinc supplementation reduces the duration and severity of both acute and persistent diarrhea [9•]. Despite the strong evidence showing that zinc supplementation reduces diarrhea in children, the impact of supplemental zinc on diarrheal morbidity in adults is unknown. The following review examines the effects of zinc on the immune response to various diarrheal pathogens.

Zinc and the immune system

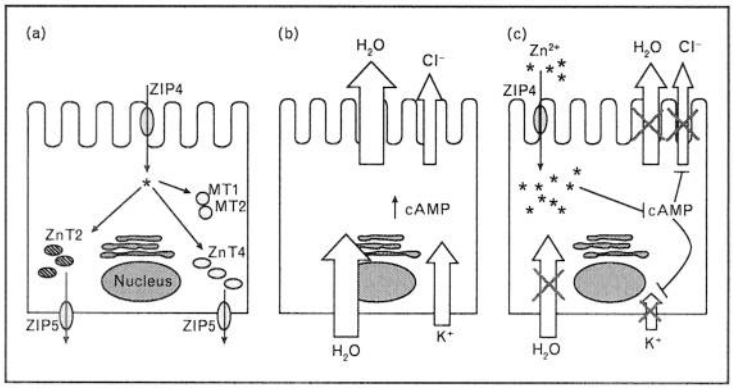
The immune-related functions of zinc have been reviewed recently [10,11]. Briefly, sub-clinical zinc deficiency impairs cellular mediators of innate immunity such as phagocytosis by macrophages and neutrophils, natural killer cell activity, generation of the oxidative burst, and complement activity [6]. These alterations contribute to increased susceptibility to infection [12]. Two phenotypically distinct T-lymphocyte populations have been identified that are zinc-sensitive: the Th1 response, important in protecting against intracellular infections and the Th2 response, important in protecting against noninvasive infections such as helminths. Adequate zinc and energy intake leads to a dominant Th1 response and a downregulated Th2 response, whereas inadequate intake of zinc and energy activates the Th2 response and downregulates the Th1 response [13,14•]. An upregulated Th1 response is more protective against many of the invasive diarrheal pathogens such as *Shigella* spp. [15]. In contrast, adequate vitamin A intake activates Th2 response and downregulates the Th1 response, whereas vitamin A deficiency reverses these patterns [16]. This differential immune regulation of micronutrient intake has distinct effects on specific stages of the natural history of infection by various pathogens, with distinct protective roles of the Th1–Th2 responses.

In-vitro studies and studies on zinc-deficient patients [10,11,17] have demonstrated that zinc plays an essential role in both cell-mediated and humoral immunity. Consistent findings in zinc deficiency are a decrease in lymphocyte numbers (lymphopenia), impaired lymphocyte development, reduced proliferation, increased apoptosis, and thymic atrophy [18]. Zinc deficiency in experimental animals is associated with low thymic weight, a progressive loss of T-lymphocytes and macrophages, delayed hypersensitivity and cytotoxic activity, impaired B and T-cell function, and reduced antibody recall responses. Zinc is an essential cofactor for the thymic hormone thymulin, which induces several T-cell markers and promotes T-cell function, including allogenic cytotoxicity, suppressor functions, and IL-2 production. It also modulates cytokine release by peripheral blood nuclear cells and induces the proliferation of CD8 T-cells, which function as cytotoxic cells able to recognize and kill pathogens [10]. In experimentally induced zinc deficiency, patients had low serum thymulin activity, impaired T-cell and natural killer cell activities, and decreased IL-2 and interferon production [19].

Zinc and mucosal cell function

Zinc also plays a key role in maintenance of gut mucosal cells. Zinc blocks basolateral potassium (K^+) channels and thus inhibits cAMP-induced chloride-dependent fluid secretion, a major control point for fluid secretions in the large intestine [20]. The mechanism(s) by which zinc may act as an enteroprotective have not yet been determined. Treatment with ORS would have its greatest effect on reducing fluid loss by increasing small intestine absorption. Zinc inhibits cAMP-induced chloride secretion by specifically inhibiting basolateral K^+ channels with no blockage of calcium-mediated K^+ channels in in-vitro studies with rat ileum [20]. Zinc also inhibits cholera toxin-induced, but not *E. coli* heat-stable enterotoxin-induced, ion secretion in cultured Caco-2 cells. One study [21] showed that cAMP acted as the intracellular effector of heat-labile enterotoxin-induced fluid secretion. Guanosine 3′,5′-cyclic monophosphate (cGMP) mediates heat-stable-induced fluid secretion. If substantiated, then the effectiveness of zinc would be limited to heat-labile-induced diarrhea or to diarrhea

Figure 1 Model for antidiarrheal action of zinc in intestinal cells



(a) Normal zinc uptake by ZIP4 transporters on the luminal surface of enterocytes. ZIP-transporters are involved in zinc uptake and localize mainly to the luminal surface; ZnT-transporters are mostly vesicular and responsible for zinc efflux and intracellular sequestration. With an adequate zinc supply, enterocytes have a greater expression of metallothioneins MT1 and MT2, and ZIP5 is localized to the basolateral membrane. (b) Movement during secretory/watery diarrhea: increased mucosal levels of cAMP induce water movement across the cell. In inflammatory diarrhea (e.g. following Shigella infection) there is also extensive histological damage to the luminal surface (not shown here). (c) Zinc action includes induction of cation absorption and/or inhibition of anion secretion; inhibition of cAMP-mediated Cl^- secretion on luminal surface, and cAMP-activated K^+ channels on basolateral membrane, reducing water loss/transit across the cell.

mediated by cAMP, but not by either cGMP or intracellular calcium. It has also been reported that the zinc transporter ZnT-1 modulates the permeation of cations through the L-type calcium channel (LTCC), thereby regulating cation homeostasis [22]. ZnT-1 may thus play a role in cellular ion homeostasis by conferring protection against pathophysiological events linked to cellular calcium or zinc permeation. A micromolar concentration of extracellular zinc could set off a massive release of calcium from intracellular pools in colonocytes. A sustained increase in intracellular calcium level may also augment K^+ efflux and a hyperpolarization of cell membrane potential, leading to an advantageous electrical gradient for chloride secretion. A model depicting the antidiarrheal action of oral zinc in intestinal cells is shown in Fig. 1.

Zinc nutriture and infectious diseases

Zinc has been demonstrated to modulate host resistance to infectious agents. A mild-to-moderate deficiency of zinc may result in profound effects on overall immune function, with increased susceptibility to diarrheal-causing pathogens (including parasites, bacteria, and viruses). Zinc deficiency in developed countries is uncommon, but groups at risk for zinc undernutrition were identified in the National Health and Nutrition Examination Survey (NHANES) III study. The groups at greatest risk of inadequate zinc intake were children (1–3 years), adolescent women (12–19 years), and elderly people aged more than 71 years [23]. In developing countries, infections often coexist with multiple nutritional deficiencies that may result from general malnutrition, especially in children and the elderly.

Results are available from a large number of RCTs of zinc supplementation in prevention of diarrhea in developing countries. The WHO/UNICEF Zinc Task Force reported a pooled analysis of 12 trials on children having acute diarrhea and four trials on children having persistent diarrhea [8]. Zinc had a positive therapeutic effect in the treatment of both acute and persistent diarrhea, that is, it is estimated that zinc supplementation reduces duration of the acute diarrhea episodes by up to 25% (compared with 24% for persistent diarrhea); zinc supplementation decreases the proportion of acute episodes lasting more than 7 days by about 25%, therefore significantly reducing the proportion of diarrhea episodes becoming persistent; and it reduces stool volume by about 30%. Subsequent trials in Bangladesh [24,25], India [26,27], and Brazil [28] corroborated these findings. A more recent meta-analysis [9•] included 16 studies that examined the efficacy and safety of supplementary oral zinc on acute diarrhea ($n = 15\,231$) and six studies that examined persistent diarrhea ($n = 2968$). Mean duration of acute diarrhea and persistent diarrhea was significantly lower for zinc compared with placebo. At day 3, presence of diarrhea was significantly lower in zinc-supplemented compared with placebo-treated volunteers in persistent diarrhea trials, but not in acute diarrhea trials. Overall, children who received zinc reported a 19 and 13% reduction in average stool frequency, 15 and 16% shortening of diarrhea duration, and a 17.9 and 18.0% probability of reducing diarrhea over placebo in acute and persistent trials, respectively. Similar to the earlier pooled Zinc Task Force analysis, the authors conclude that zinc supplementation reduces the duration and severity of acute and persistent diarrhea in children.

Although there are many causes of chronic diarrhea, these may be different for children and adults. Causes of chronic diarrhea are typically grouped into two general categories; that which is caused by an infection and diarrhea that is not caused by an infection. Pathogen-negative diarrhea is the most likely cause of traveler's diarrhea without a definable cause [29]. Adult 'travelers' with acute diarrhea, treated with the antibiotic rifaximin [Xifaxan (Salix Pharmaceuticals, Inc., Morrisville, North Carolina, USA) 200 mg three times a day for 3 days], were assessed in two double-blind, placebo-controlled RCTs. Among pathogen-negative patients, rifaximin was more effective than placebo for median time-to-last-stool (33 vs. 68 h), mean number of unformed stools passed (6.5 vs. 8.6), and clinical wellness (77 vs. 61%). Thus, for pathogen-negative diarrhea, rifaximin appears to be an effective treatment with no concurrent side effects. Conversely, infectious-diarrheal disease may be caused by a variety of parasites, bacteria, and/or viruses, with a distinct paucity of available antidiarrheal vaccines. Currently, nontyphoid *Salmonella*, *E. coli* O157:H7, and *Campylobacter* are among the most prevalent causes of food-borne illness in the USA [30].

Zinc and parasitic diarrhea

The following is a review of RCTs involving zinc supplementation in various populations. This review focuses on specific diarrheal pathogens to provide strong evidence for a causal relationship between zinc supplementation and a significantly reduced incidence of pathogen-specific diarrhea.

Intestinal protozoan infections by *Giardia* and *Cryptosporidium* are common in humans worldwide. Especially important are infections in children, during pregnancy, and among individuals with HIV/AIDS. Associated morbidity and mortality are high, with more than 58 million cases of childhood protozoal diarrhea each year. Direct costs of management alone are estimated at approximately US$150 million [31]. It is estimated that 1.5 billion people harbor *Ascaris lumbricoides*, 478 million of whom are children (<15 years of age). Also, there are approximately 2.8 million *Giardia lamblia* infections per year. Recurrent asymptomatic and symptomatic infections by these and other intestinal parasites among young children can have long-term effects on overall growth and development. A recent study conducted on children residing in Mexico City [14•] reported that vitamin A and zinc (20 mg of elemental zinc as zinc methionine, daily for 1 year) reduced *G.lamblia* incidence, whereas zinc supplementation alone decreased *Entamoeba histolytica*-associated diarrhea. With no comparable studies on adult populations, it remains to be determined which of these diarrheal pathogens might respond to zinc supplementation and whether age-related differences in response to dietary zinc may minimize success in adult populations.

Zinc and bacterial diarrhea

Enteric pathogens constitute a major pediatric threat in the developing world through their impact on morbidity and mortality and impairment of physical and cognitive development. It appears likely that a cause-and-effect relationship exists with malnutrition. Although many bacterial pathogens can cause diarrheal diseases, a group of fewer than 10 (including *Shigella* spp., *ETEC*, *Vibrio cholerae*, and possibly *Campylobacter jejuni*) account for a significant percentage of these diseases in developing countries. Vaccines against these agents offer a potentially effective control measure against these diseases, but safe, practical, and effective vaccines for many of these agents have yet to be realized. Zinc supplementation has been shown to reduce the duration and severity of watery diarrhea in studies worldwide, but its mode of action is not known. Initially, it was believed that zinc was acting to correct or ameliorate zinc deficiency, but this appears not to be the only means of protection because children and animals that are not zinc deficient still benefited from zinc in studies of diarrhea. Recently, Crane *et al.* [32•] reported that zinc decreased adherence of enteropathogenic *E. coli* (EPEC) bacteria to rabbit intestinal epithelium. They also demonstrated that zinc inhibited a key enzyme, ecto-5′-nucleotidase, involved in the conversion of 5′-AMP to adenosine in the lumen of the intestine. Adenosine triggers fluid secretion from host intestinal cells and also has growth-promoting effects on EPEC bacteria. The zinc inhibition reduced the secretory response that triggers *EPEC*-activated watery diarrhea. The authors concluded that these effects should be considered pharmacologic effects of zinc, not zinc-replacement therapy, as they also occur in the absence of zinc deficiency.

Cholera is a common disease in many countries of the world. About 230 000 cases in more than 50 countries are reported globally, but the WHO estimates that official notifications make up only approximately 5% of the real burden of cholera [33]. This means that as many as three million cases and more than 100 000 deaths occur each year. About 85% of episodes are mild-to-moderate in severity. In animal studies, the net water and sodium secretion induced by cholera toxin was four times greater in zinc-deficient compared with zinc-adequate animals. Furthermore, zinc repletion of the zinc-deficient animals elicited a 40% reduction in secretion within 48 h of zinc repletion [34]. Recently, Roy *et al.* [35•] investigated the impact of zinc on severe diarrhea in children caused by cholera. Children, aged 3–14 years with watery diarrhea that was confirmed positive by stool culture for *V.cholerae*, received either 30 mg elemental zinc per day as zinc

acetate, or placebo until recovery. All children received erythromycin suspension orally in a dose of 12.5 mg/kg every 6 h for 3 days. More patients in the zinc group than in the control group recovered within 2 (49 vs. 32%) or 3 (81 vs. 68%) days. Zinc-supplemented children had 12% shorter duration of diarrhea than control patients (64 vs. 73 h) and 11% less stool output. The authors concluded that zinc supplementation was beneficial in reducing the duration of diarrhea and stool output in children with cholera.

Shigella is a major cause of childhood morbidity and mortality globally, causing bacillary dysentery in humans, and an acute rectocolitis that reflects the capacity of the microorganism to disrupt, invade, and trigger the inflammatory destruction of the intestinal epithelium. Shigellosis typically manifests as bloody-mucoid stools and/or febrile diarrhea. *Shigella sonnei* persists in developed (and transitional) countries, causing sporadic diarrhea and occasional outbreaks in epidemiological niches (such as day-care centers) where personal hygiene can be suboptimal. Travelers from developed to developing regions, who mainly acquire *S. sonnei* and *S. flexneri* infections, represent a target population for *Shigella* vaccines. Levine *et al.* [36] reviewed the most advanced strategies for *Shigella* vaccine development and the factors that have impeded *Shigella* vaccine development. Meanwhile, Roy *et al.* [37•] reported on a RCT using zinc (20 mg/day elemental zinc given as zinc acetate, daily for 2 weeks) to manage shigellosis in malnourished children. Additionally, all children received pivmecillinam (15 mg/kg every 6 h for 5 days). The authors report that children receiving zinc recovered from acute illness significantly faster than the control children ($P < 0.05$). The median time (in days) to recovery and disappearances of blood and mucous was significantly shorter in the zinc-supplemented group (50%) compared with the control group. The mean body weight of zinc-supplemented children increased significantly from 8.8 kg on admission to 9.2 kg at recovery ($P < 0.01$), which was not observed in the control children. During the 6-month follow-up period, zinc-supplemented children had significantly fewer mean episodes of diarrhea compared with the control children (2.2 vs. 3.3; $P = 0.03$). They concluded that zinc supplementation significantly shortens the duration of acute shigellosis, promotes better weight gain during recovery, and reduces diarrheal morbidity during the subsequent 6 months.

Zinc and viral diarrhea

Rotavirus infection is the most common cause of severe diarrhea disease in children less than 5 years worldwide and continues to have a major global impact on childhood morbidity and mortality. In 2006, two new (live, oral, attenuated) vaccines against rotavirus were licensed, RotaTeq (Merck, Whitehouse Station, New Jersey, USA) and Rotarix (GSK, Research Triangle Park, North Carolina, USA). Both vaccines demonstrated very good safety and efficacy profiles in large RCTs in western industrialized countries and in Latin America [38]. These new rotavirus vaccines offer the best hope of reducing the toll of acute rotavirus gastroenteritis in both developed and developing countries. With the development of such vaccines, the need for micronutrient interventions, specifically zinc-supplementation studies, is not required.

Vaccines against other viral-diarrheal pathogens offer a potentially effective control measure against these diseases, but safe, practical, and effective vaccines for many viral-diarrhea pathogens have yet to be realized. Although the use of highly active antiretroviral therapies (ART) has dramatically decreased the morbidity and mortality of HIV-1 infections, the major goal of HIV/AIDS research still eludes us: the development of a safe and effective vaccine [39]. Meanwhile, the side effects of HIV therapy are common and include diarrhea caused by protease inhibitors [40]. Several studies in industrialized countries have found an association between HIV disease progression and low blood concentrations of zinc [41]. There is concern that inadequate intake of nutrients may compound the susceptibility to secondary infection and thereby cause a further worsening of immune function in HIV-positive persons. Recent studies report no beneficial effects of zinc supplementation for persistent diarrhea in children [42] or adults [41] with HIV infections. In the study of HIV-infected children [42], neither zinc [10 mg zinc as gluconate daily for 18 months] combined with vitamin A nor zinc and vitamin A combined with other micronutrients reduced diarrhea morbidity. Two key issues with the design of this study may explain the reported outcome: the study did not include a placebo group (vitamin A alone) and shortly after study enrollment began, the host-country government implemented regulations requiring the fortification of maize meal and wheat flour, including flour used by bakeries, with zinc and other micronutrients. The amount of fortification (up to 30 mg zinc/kg of maize meal) in the staple foods may have improved micronutrient status in children with access to commercially produced meal or bread [43]. In the study of HIV-infected adults [41], zinc supplementation [50 mg of elemental zinc as zinc sulphate, twice daily for 14 days] reportedly had no significant effect on the duration or remission of diarrhea. Several study design limitations may explain these outcomes: 83% of patients had CD4 values less than 200 cells/μl (range 0–909) – patients with CD4 values less than 200 cells/μl may benefit substantially better from aggressive ART until their CD4 values are greater than 250 cells/μl; the zinc-supplementation trial was too short (14 days) and the dose provided was excessive as 100 mg elemental zinc/day was provided, despite the upper limit

for elemental zinc set at 40 mg/day for adults [44]; and the supplement was provided as zinc sulphate heptahydrate – the Material Safety Data Sheet (MSDS) for $ZnSO_4.7H_2O$ states that 'if ingested, it will cause diarrhea'.

Despite those studies indicating that diarrhea is non-responsive to zinc supplementation in individuals with HIV-1, recent in-vitro evidence supports a 'zinc approach' for treating diarrhea in HIV-infected patients. Canani *et al.* [45•] report that the transactivating peptide Tat (produced by HIV-1) is involved in the pathogenesis of diarrhea in AIDS patients and that zinc prevented Tat-induced fluid secretion, directly limiting a specific mechanism of HIV-related diarrhea. Differences in reported responses to supplemental zinc between children with diarrhea and adults with HIV-infection and diarrhea could also reflect age-dependent differences in zinc homeostasis, host immune response, inclusion criteria, or supplementation regimen. Alternatively, they could reflect the possibility that low plasma concentrations of zinc in persons with HIV-infection do not reflect true zinc deficiency. Supplementation of HIV-infected patients with dietary reference intake levels of zinc is prudent, but high doses should be discouraged. Although individuals with HIV infection are expected to benefit from zinc supplementation, the virological and immunological consequences of zinc for replication of the virus need careful assessment. Both the viral nucleocapsid and integrase proteins, essential for assembly of infectious virions, contain zinc fingers that require zinc for normal structure and function. In addition, zinc activates lymphocytes [46], and activated CD4 T-lymphocytes are major target cells for HIV-1 replication and an increase could potentially enhance HIV-1 replication. If mass supplementation with zinc is to be recommended in areas with a high prevalence of HIV-infection, the safety of this intervention needs to be established. A recent trial of zinc supplementation in HIV-infected children was conducted to assess the effect on plasma HIV-1 viral load and infectious disease morbidity [47]. Zinc supplementation (10 mg of elemental zinc daily for 6 months) did not increase plasma HIV-1 viral load and thus could reduce morbidity caused by diarrhea. The outcomes of these studies suggest that programs to enhance zinc intake in deficient populations with a high prevalence of HIV-infection can be implemented without concern for adverse effects on HIV-1 replication.

Thus, the combination of ART, a healthy diet, and a low-dose multivitamin/mineral supplement may be especially effective in the treatment of HIV-infected patients [48]. Future research on HIV-associated diarrhea in adults should assess more potentially effective antimicrobial interventions, in combination with zinc supplementation. Information from these additional studies will help facilitate guidelines for empiric antimicrobial treatment algorithms.

Conclusion

Oral zinc can correct a common micronutrient deficiency in children with diarrhea [1]. Large intervention RCTs with daily intakes of 10–30 mg of zinc have shown that zinc supplementation could be an important adjuvant therapy for treating diarrhea in children in developing countries, and by inference, these trials should be extended to include adults. This review would be incomplete if we did not acknowledge the lack of success in zinc-supplementation studies conducted in countries where the diarrheal pathogens are not zinc-responsive, which may in part be due to distinct parasite-specific health outcomes. A recent study in Mexico City [14•] demonstrated that vitamin A and zinc reduced *G.lamblia* incidence, whereas zinc supplementation increased *A. lumbricoides* incidence but decreased *E. histolytica*-associated diarrhea.

Future studies must, therefore, be designed to allow for diarrheal-pathogen identification, which could lead to elucidation of potential zinc-specific benefits and diversity in the study population groups to include the elderly, immunocompromised patients, and other community settings. Further, carefully conducted RCTs are necessary to confirm (or refute) the efficacy of zinc against both acute and persistent diarrhea in adults, and such trials may be of high economic value.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 803–804).

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